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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,501	05/23/2001	Robert P. Kimberly	UAB-14402/22	9412

7590 01/28/2004

Ellen S Cogen
Gifford Krass Groh Sprinkle Anderson & Citkowski
Suite 400
280 N Old Woodward Avenue
Birmingham, MI 48009-5394

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,501	KIMBERLY, ROBERT P.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 24-32* is/are pending in the application.

4a) Of the above claim(s) *4,6,8-10,12-19,21 and 24-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7,11 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the response dated 10/31/2003 is acknowledged. The traversal is on the ground(s) that the claims relating to Fas ligand promoter polymorphs, claims 1-21, have not been identified as having separate classification, separate status in the art, or different field of search. This argument was not found persuasive. Firstly, the instant case is a 371 application, and the examiner followed the proper guidelines for restricting in 371 applications. Further, the different inventions do in fact encompass a different field of search and a separate classification according to the Manual of Patent Classification. For example the claims to methods are classified in 435/6 while the polynucleotides are classified in 536/23.1. These inventions represent claims in separate classes, let alone separate subclasses. In addition, searching the type of claims submitted in the instant application requires keyword searching in the not patent literature, as well as classification searching in the patent literature. Even if the inventions were classified in the same classes, the different claims represent polymorphisms at different positions wherein a search of one polymorphism would not necessarily provide references with regard to another polymorphism. Also, while the claims recite "haplotype", no specific haplotype has been set forth in any of the claims. At most, claim 5 sets forth 4 different polymorphisms, however they are claimed singly, and not in any combination, let alone any particular combination. The argument that all polymorphs function in Fas ligand promoter is also not found persuasive because the claims set forth different effects for the polymorphs or haplotypes. For example, claim 3 recites the polymorph binds NF-IL6, while claim 4 recites that the polymorph binds TCF/LEF-1. Such claims represent entirely different

searches with regard to the non patent literature. With regard to the citation of the partial waiver of 37 CFR 1.41 per 1192 OG 68, it is noted that such states that "up to 10" sequences can be searched. Due to the size of the sequence databases and the time it takes to search a single sequence in Genbank, for example, searching 10 patentably distinct sequences is no longer considered a 'reasonable' search and poses a significant burden on the office. It is also noted that the partial waiver is with regard to the recitation of SEQ ID NOS in claims. None of the elected claims recite any SEQ ID NOS. Upon examining the specification, it appears that the polymorphism at position –844 is involved in binding of NF-IL6, therefore, claim 5, as it pertains to –844 and claim 7 will be rejoined with Group I.. The requirement is still deemed proper and is therefore made FINAL.

2. An action on the merits of claims 1-3, 5, 7, 11, and 20, with regard to NF-IL6 and detection of a polymorphism at position –844 follows.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claim 20 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 5, 7, 11, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

Nature of the Invention

The claims are broadly drawn to determining susceptibility to any autoimmune disease or any cancer by haplotyping a Fas ligand promoter "region", wherein haplotyping further encompasses a polymorph. The claims are further drawn to a polymorph being one that is active in binding NF-IL6 transcription factor as well as a polymorph at position –844.

Amount of Direction and Guidance

The specification teaches several genotype frequencies with regard to 4 polymorphic position in the Fas ligand promoter in population studies of Caucasian and African Americans. The specification does not teach any specific haplotypes that indicate increased susceptibility to any autoimmune disease, any cancer, any specific autoimmune disease or any specific cancer. The specification does not teach any specific haplotypes that contain polymorphisms that bind NF-IL6 transcription factor. While the specification teaches a luciferase assay with regard to different a T and a C allele at position –844 and that the C allele showed almost twice the activity than the T allele, the specification does not teach how such is correlated to binding of NF-IL6 or how any other allele would also be associated with binding such that the skilled artisan would be able to predictably determine alleles in the Fas ligand promoter 'region' which would be active in binding NF-IL6.

In addition, the claims are drawn to haplotyping in a 'region' wherein the specification does not define the metes and bounds of said region. Therefore, the claims broadly encompass haplotypes or SNPs that contain alleles outside of the Fas ligand promoter, however the specification has not set forth any predictable correlation with regard to haplotypes or SNPs containing such alleles and any specific or general autoimmune disease or cancer.

In addition, the claims are drawn to determining any autoimmune disease or cancer by simply haplotyping the Fas ligand promoter. However, the specification has set forth no predictable correlation that a SNP or particular haplotype is associated with increased or decreased susceptibility to autoimmune diseases or cancer in general. The terms "autoimmune disease" and "cancer" encompass an extremely large number of diseases and disorders, which

have very different symptoms, causes (if known), and course of illness. Autoimmune diseases encompass such diseases as SLE (systemic lupus erythematosus) and Rheumatoid arthritis, for example, while cancers encompass leukemias, hepatocellular cancers, colorectal cancers, lung cancers, breast cancer, prostate cancer, etc. However, the specification provides no teaching or demonstration that patients with any specific haplotype or SNP would be susceptible to *any* autoimmune disease or cancer. The specification makes the general statement that the Fas ligand was found to be expressed in human melanoma, hepatocellular carcinoma, lung cancer, astrocytoma, esophageal carcinoma, and various other cancer, such teaching is not an indication that Fas ligand is necessarily involved in cancer, because many genes and proteins are expressed in cancer, without being directly or indirectly involved in such. In addition, although the specification teaches certain alleles at the SNP at position –844 occur with different frequencies in SLE vs RA, these frequencies are very different from each other and provide no predictable correlation that a specific allele or haplotype can generally be extrapolated to be associated with any autoimmune disease or any cancer.

Level of predictability and unpredictability in the art

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. teaches that they were unable to confirm an association between a gene

polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Further, in some cases where multiple polymorphisms were identified in a gene, some of these were demonstrated to be disease associated and some were not. For example, Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma Blumenfeld et al found that some of these polymorphisms are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined not to have a statistical association with asthma (p=0.294). Thus, the art teaches that even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Presence and Absence of Working Examples

In the instant case, the polymorphism at position –844, and its incidence in different haplotypes was analyzed in different population samples. Statistically significant differences were found with regard to the occurrence of different genotypes in Caucasian vs African American populations, however such analysis does not predictably establish a correlation

between a specific genotype and a any autoimmune disease or cancer in general, or even any specific autoimmune disease or cancer. Further, Table 5 shows "putative" or assumed haplotypes for SNPs of the 5' Fas ligand promoter region. The use of the term "putative" makes it unclear as to how such data was obtained. For example, was this an actually study and the numbers reflect the actual data from the study or were the numbers inferred from a different study or method of analysis. In addition, from the recitation in the tables it is clear that very different frequencies of haplotypes and genotypes occurs in two different autoimmune diseases. For example, a C at position –844 occurs in 63% of normal controls in the CAAC haplotype. As compared to these controls, only 44% of SLE patients possess the same allele, while 73% of RA (rheumatoid arthritis, an autoimmune disease) patients possess this allele. On the other hand in the TATC haplotype, a T allele at –844 is found in 12% of controls and only 5% of SLE patients but in 17% of RA patients. From this data it is completely unpredictable as to whether the occurrence of any particular haplotype or genotype increases or decreases an individual's susceptibility to any autoimmune disease. Further, the specification provides no analysis as to whether such data is statistically significant.

With regard to the –844 allele, the specification teaches (page 35) that the C allele had twice the promoter activity than the T allele in a luciferase reporter assay. It is unclear, however, how such activity relates to binding of C/EBPB (NF-IL6). The specification further states that the low affinity allele (-844T) was over represented in patients with SLE (lines 15-18). The significance of this statement is unclear, however, because the teachings of Table 5 show that in one haplotype, TAAC, 42% of SLE patients had the T allele while only 24% of controls had the allele, but that in a different haplotype, TATC, the T allele was *underrepresented* in that 5% of

SLE patients had the "low affinity allele" while 12% of controls had the allele. Therefore, it appears that the teachings of table 5 contradict the statement in the specification as to overrepresentation of the T allele in SLE patients. Further, if the term "overrepresentation" was with regard to 44% of SLE patients having the C allele and 56% of SLE patients having the T allele in table 5, without a teaching of the statistical significance of such data, the skilled artisan would be unable to establish predictable correlation with regard to the occurrence of a T at position –844 or any specific haplotype and susceptibility to autoimmune diseases or cancer in general or with any specific autoimmune disease or cancer.

The specification provides no analysis of any polymorphism in general, one that binds NF-IL6, or position –844 in the Fas ligand promoter in any patients vs controls with any type of cancer.

Quantity of Experimentation Necessary

Therefore, due to the lack of guidance from and unpredictability taught in the specification and the unpredictability taught in the art, undue experimentation would be required of the skilled artisan to practice the claimed invention. To practice the invention as claimed, the skilled artisan would be required to perform an analysis of each position within the Fas ligand promoter as well as a large region around it, to determine whether or not such positions are polymorphic and to determine which positions were 'active' in binding NF-IL6. Once such polymorphic positions were found, the skilled artisan would then have to determine genotype and different haplotype frequencies in large number of different samples of patients with many different autoimmune diseases and cancers, vs controls to determine if any SNPs or haplotypes

conferred susceptibility to autoimmune diseases and cancers in general, or any specific autoimmune disease or cancer. Such analysis would require an extremely large amount of unpredictable trial and error analysis. As both the specification and the art demonstrate that the outcome of such analysis is highly unpredictable, such experimentation is considered undue.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-3, 5, 7, 11, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite as the final process step does not correlate back to the preamble of the claim. The preamble states a method for determining autoimmune disease or cancer susceptibility however the only step in the method is haplotyping an individual in a Fas ligand promoter region. Therefore it is unclear whether the claim is drawn to a method for determining autoimmune disease or cancer susceptibility or haplotyping an individual. It is unclear how only haplotyping the Fas ligand promoter determines disease susceptibility as one would expect that healthy subjects would have some sort of Fas ligand promoter haplotype. The metes and bounds of the claim are unclear.

Claim 1 is indefinite in the recitation of "Fas ligand promoter *region*" as it is unclear if haplotyping occurs only in the promoter or includes an undefined *region* around the promoter. If the latter is the case, it is further unclear what is encompassed by the term 'region'. As neither

the specification nor the claims define the requisite degree encompassed by the term "region", the metes and bounds of the claim are unclear.

Claims 2, 3, 5 and 20 recites the term "polymorph" which is not specifically defined in the specification, but appears to be drawn to a "polymorphism". As the instant specification appears to be a translation, the term should be amended to recite "polymorphism" to agree with the current English designation for the term.

Claims 7 and 11 lack sufficient antecedent basis for the term "said nucleotide site" as the term "nucleotide site" does not appear anywhere in claims 1, 7, or 11.

Claim 20 provides for the use of a single nucleotide polymorph, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Conclusion

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0572. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Jehanne Sitton
Primary Examiner
Art Unit 1634

Jehanne Sitton
1/26/04